GLI3 gene

GLI family zinc finger 3

Normal Function

The *GLI3* gene belongs to a family of genes that are involved in the normal shaping (patterning) of many tissues and organs during the early stages of development before birth. To carry out this role, proteins produced from genes in the GLI family attach to specific regions of DNA and help control whether particular genes are turned on or off (gene expression). GLI proteins are called transcription factors on the basis of this action.

Proteins in the GLI family function in the same molecular pathway as a protein called Sonic Hedgehog. This pathway is essential for early development. It plays a role in cell growth, cell specialization, and the patterning of structures such as the brain and limbs. Depending on signals from Sonic Hedgehog, the GLI3 protein can either turn on (activate) or turn off (repress) other genes. Researchers are working to identify the genes targeted by the GLI3 protein during development.

Health Conditions Related to Genetic Changes

acrocallosal syndrome

At least two mutations in the *GLI3* gene have been reported in people with features of acrocallosal syndrome, a rare condition characterized by certain brain abnormalities, extra fingers and toes (polydactyly), and distinctive facial features, including widely spaced eyes (hypertelorism) and a prominent forehead. These signs and symptoms overlap significantly with those of Greig cephalopolysyndactyly syndrome (described below), so acrocallosal syndrome resulting from *GLI3* gene mutations is sometimes considered a severe form of that condition.

The *GLI3* gene mutations that cause acrocallosal syndrome change single protein building blocks (amino acids) in a particular region of the GLI3 protein, which disrupts the protein's function. The malfunctioning protein likely alters the expression of certain genes during early development. The role of the GLI3 protein in brain and limb patterning may help explain why mutations lead to brain abnormalities, polydactyly, and the other features of acrocallosal syndrome.

Greig cephalopolysyndactyly syndrome

At least 120 mutations in the *GLI3* gene have been identified in people with Greig cephalopolysyndactyly syndrome, which is a rare condition characterized by polydactyly, hypertelorism, a broad forehead, and an unusually large head

(macrocephaly). The genetic changes associated with Greig cephalopolysyndactyly syndrome include insertions or deletions of a small amount of DNA and changes in single DNA building blocks (base pairs) in critical regions of the gene. This condition can also be caused by chromosomal abnormalities involving the region of chromosome 7 that contains the *GLI3* gene. The genetic changes that cause Greig cephalopolysyndactyly syndrome prevent one copy of the gene in each cell from producing any functional GLI3 protein. As a result, only half the normal amount of this protein is available to control the expression of target genes during early development. It remains unclear how a reduced amount of the GLI3 protein disrupts development of the limbs, head, and face and causes the specific features of Greig cephalopolysyndactyly syndrome.

Pallister-Hall syndrome

More than 40 mutations in the *GLI3* gene have been found to cause Pallister-Hall syndrome, a rare condition whose major features include polydactyly, an abnormal growth in the brain called a hypothalamic hamartoma, and a malformation of the airway called a bifid epiglottis. Most of the mutations that cause Pallister-Hall syndrome occur near the middle of the gene, creating a premature stop signal in the instructions for making the GLI3 protein. As a result, cells produce an unusually short version of the protein. Unlike the full-length GLI3 protein, which can turn target genes on or off, the short protein can only repress the expression of target genes. Although this change clearly disrupts embryonic development, it is not known how the altered function of the GLI3 protein leads to the varied signs and symptoms of Pallister-Hall syndrome.

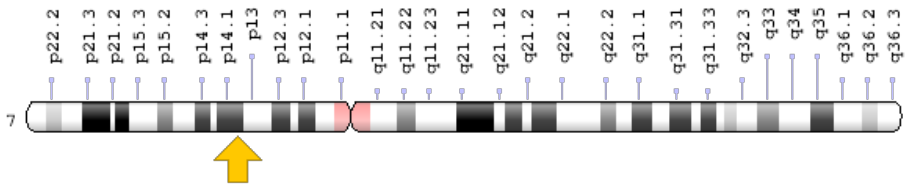
other disorders

Mutations in the *GLI3* gene have been found in people who have polydactyly without the other features of acrocallosal syndrome, Greig cephalopolysyndactyly syndrome, or Pallister-Hall syndrome (described above). These cases are described as isolated or nonsyndromic because the polydactyly occurs without other signs and symptoms. *GLI3* gene mutations can cause several forms of isolated polydactyly. These include postaxial polydactyly type A (PAP-A) and type A/B (PAP-A/B), which are characterized by an extra digit next to the little finger or the small toe. *GLI3* gene mutations can also cause preaxial polydactyly type IV (PPD-IV), which is characterized by extra digits next to the thumb or big toe (hallux) and fused skin between some fingers and toes (cutaneous syndactyly). PPD-IV also can include extra digits in other positions on the hands or feet. The pattern of polydactyly seen with PPD-IV is similar to that of Greig cephalopolysyndactyly syndrome, and some researchers suggest that PPD-IV may be a very mild form of that syndrome.

Chromosomal Location

Cytogenetic Location: 7p14.1, which is the short (p) arm of chromosome 7 at position 14.1

Molecular Location: base pairs 41,960,949 to 42,237,019 on chromosome 7 (Homo sapiens Annotation Release 108, GRCh38.p7) (NCBI)



Credit: Genome Decoration Page/NCBI

Other Names for This Gene

- ACLS
- GCPS
- GLI-Kruppel family member GLI3 (Greig cephalopolysyndactyly syndrome)
- GLI3_HUMAN
- oncogene GLI3
- PAP-A
- PAPA
- PAPA1
- PAPB
- PHS
- PPDIV
- zinc finger protein GLI3

Additional Information & Resources

Educational Resources

- Developmental Biology (sixth edition, 2000): The Hedgehog Pathway https://www.ncbi.nlm.nih.gov/books/NBK10043/#A1063

GeneReviews

- Greig Cephalopolysyndactyly Syndrome
  https://www.ncbi.nlm.nih.gov/books/NBK1446
- Pallister-Hall Syndrome
  https://www.ncbi.nlm.nih.gov/books/NBK1465

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28GLI3%5BTIAB%5D%29+OR+%28GLI-Kruppel+family+member+GLI3%5BTIAB%5D%29%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D

OMIM

- GLI-KRUPPEL FAMILY MEMBER 3
  http://omim.org/entry/165240
- POLYDACTYLY, POSTAXIAL, TYPE A1
  http://omim.org/entry/174200
- POLYDACTYLY, PREAXIAL IV
  http://omim.org/entry/174700

Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology
  http://atlasgeneticsoncology.org/Genes/GC_GLI3.html
- ClinVar
  https://www.ncbi.nlm.nih.gov/clinvar?term=GLI3%5Bgene%5D
- HGNC Gene Family: Zinc fingers C2H2-type
  http://www.genenames.org/cgi-bin/genefamilies/set/28
- HGNC Gene Symbol Report
  http://www.genenames.org/cgi-bin/gene_symbol_report?q=data/hgnc_data.php&hgnc_id=4319
- NCBI Gene
  https://www.ncbi.nlm.nih.gov/gene/2737
- UniProt
  http://www.uniprot.org/uniprot/P10071

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